# General

## Guideline Title

Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline.

## Bibliographic Source(s)

Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31. [213 references] PubMed

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

# Recommendations

## Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and for the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Treatment Goals for Cushing's Syndrome

In patients with overt Cushing's syndrome (CS), the Task Force recommends normalizing cortisol levels or action at its receptors to eliminate the signs and symptoms of CS and treating co-morbidities associated with hypercortisolism. (1|+++O)

The Task Force recommends against treatment to reduce cortisol levels or action if there is not an established diagnosis of CS. (1|+OOO)

The Task Force suggests against treatments designed to normalize cortisol or its action when there is only borderline biochemical abnormality of the hypothalamic-pituitary-adrenal (HPA) axis without any specific signs of CS. The benefit of treating to normalize cortisol is not established in this setting. (2|+OOO)

Optimal Adjunctive Management

The Task Force recommends providing education to patients and their family/caretaker(s) about their disease, treatment options, and what to expect after remission. (Ungraded best practice statement)

The Task Force recommends that all patients receive monitoring and adjunctive treatment for cortisol-dependent comorbidities (psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness). (Ungraded best practice

statement)

The Task Force recommends that a multidisciplinary team, including an experienced endocrinologist, takes patient values and preferences into consideration and provides education about the treatment options to the patient. (Ungraded best practice statement)

The Task Force suggests evaluating CS patients for risk factors of venous thrombosis. (2|++OO)

In patients with CS undergoing surgery, the Task Force suggests perioperative prophylaxis for venous thromboembolism. (2|++OO)

The Task Force recommends that clinicians discuss and offer age appropriate vaccinations to CS patients-particularly influenza, *Herpes zoster*, and pneumococcal vaccinations - due to an increased risk of infection. (Ungraded best practice statement)

First-Line Treatment Options

The Task Force recommends initial resection of primary lesion(s) underlying Cushing's disease (CD), ectopic and adrenal (cancer, adenoma, and bilateral disease) etiologies, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess (see Figure 1 in the original guideline document). (1|++++)

The Task Force recommends unilateral resection by an experienced adrenal surgeon for all cases of benign unilateral disease. (1|+++O)

The Task Force recommends localizing and resecting ectopic adrenocorticotropic hormone (ACTH)-secreting tumors with node dissection as appropriate. (1|++++)

The Task Force recommends transsphenoidal selective adenomectomy (TSS) by an experienced pituitary surgeon as the optimal treatment for CD in pediatric and adult patients. (1|++++)

The Task Force recommends measuring serum sodium several times during the first 5–14 days after TSS. (1|++OO)

The Task Force recommends assessing free thyroxine ($T_4$) and prolactin within 1–2 weeks of surgery, to evaluate for overt hypopituitarism. (1|++OO)

The Task Force recommends obtaining a postoperative pituitary magnetic resonance imaging (MRI) scan within 1–3 months of successful TSS. (Ungraded best practice statement)

The Task Force recommends surgical resection of bilateral ad renal disorders (1|++OO) and suggests medical therapy to block aberrant hormone receptors for bilateral macronodular adrenal hyperplasia (BMAH) (2|++OO).

Remission and Recurrence after Surgical Tumor Resection

The Task Force suggests an individualized management approach based on whether the postoperative serum cortisol values categorize the patient's condition as hypocortisolism, hypercortisolism, or eucortisolism. (Ungraded best practice statement)

The Task Force recommends additional treatments in patients with persistent overt hypercortisolism. (1|++++)

The Task Force recommends measuring late-night salivary or serum cortisol in patients with eucortisolism after TSS, including those cases where eucortisolism was established by medical treatment before surgery. (1|++OO)

The Task Force recommends using tests to screen for hypercortisolism to assess for recurrence in patients with ACTH-dependent CS. (1|+++O)

Glucocorticoid Replacement and Discontinuation, and Resolution of Other Hormonal Deficiencies

The Task Force recommends that hypocortisolemic patients receive glucocorticoid replacement and education about adrenal insufficiency after surgical remission. (1|++++)

The Task Force recommends follow-up morning cortisol and/or ACTH stimulation tests or insulin-induced hypoglycemia to assess the recovery of the HPA axis in patients with at least one intact adrenal gland, assuming there are no contraindications. The Task Force also recommends discontinuing glucocorticoid when the response to these test(s) is normal. (1|+++O)

The Task Force recommends reevaluating the need for treatment of other pituitary hormone deficiencies in the postoperative period. (1|+++O)

Second-Line Therapeutic Options

In patients with ACTH-dependent CS who underwent a noncurative surgery or for whom surgery was not possible, the Task Force suggests a

shared decision-making approach because there are several available second-line therapies (e.g., repeat TSS, radiation therapy [RT], medical therapy, and bilateral adrenalectomy). (2|++OO)

The Task Force suggests bilateral adrenalectomy for occult or metastatic ectopic ACTH secretion (EAS) or as a life-preserving emergency treatment in patients with very severe ACTH-dependent disease who cannot be promptly controlled by medical therapy. (2|+++O)

The Task Force recommends regularly evaluating for corticotrope tumor progression using pituitary MRIs and ACTH levels in patients with known CD who undergo bilateral adrenalectomy and in patients who undergo this procedure for presumed occult EAS (because some of the latter have a pituitary and not ectopic tumor). (1|+++O)

Repeat Transsphenoidal Surgery

The Task Force suggests repeat TSS, particularly in patients with evidence of incomplete resection, or a pituitary lesion on imaging. (2|++OO)

Radiation Therapy/Radiosurgery for CD

The Task Force recommends confirming that medical therapy is effective in normalizing cortisol before administering radiation RT/radiosurgery (RS) for this goal because this will be needed while awaiting the effect of radiation. (1|+OOO)

The Task Force suggests RT/RS in patients who have failed TSS or have recurrent CD. (2|++OO)

The Task Force recommends using RT where there are concerns about the mass effects or invasion associated with corticotroph adenomas. (1|+++O)

The Task Force recommends measuring serum cortisol or urine free cortisol (UFC) off-medication at 6- to 12-month intervals to assess the effect of RT and also if patients develop new adrenal insufficiency symptoms while on stable medical therapy. (1|+++O)

Medical Treatment

The Task Force recommends steroidogenesis inhibitors under the following conditions: as second-line treatment after TSS in patients with CD, either with or without RT/RS; as primary treatment of EAS in patients with occult or metastatic EAS; and as adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma (ACC). (1|+++O)

The Task Force suggests pituitary-directed medical treatments in patients with CD who are not surgical candidates or who have persistent disease after TSS. (2|+++O)

The Task Force suggests administering a glucocorticoid antagonist in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after TSS. (2|+++O)

The Task Force suggests targeted therapies to treat ectopic ACTH syndrome. (2|+OOO)

Approach for Long-Term Follow-up

The Task Force recommends treating the specific comorbidities associated with CS (e.g., cardiovascular risk factors, osteoporosis and psychiatric symptoms) in all patients with CS throughout their lives until resolution (see Figure 1 in the original guideline document). The Task Force also recommends testing for recurrence throughout life, except in patients who underwent resection of an adrenal adenoma with a computerized tomography (CT) density of <10 Hounsfield units. (1|+++O)

The Task Force recommends educating patients and families about the clinical features of remission. (Ungraded best practice statement)

In patients with adrenal adenoma, the Task Force suggests follow-up tests for the specific comorbidities associated with CS if the adenoma density on CT was < 10 Hounsfield units. (2|++OO) For those with higher Hounsfield unit values or pathology consistent with possible carcinoma, the Task Force suggests evaluating for malignancy using imaging. (2|+OOO)

The Task Force recommends that patients with Carney complex have lifelong follow-up tests for cardiac myxoma and other associated disease (testicular tumors, acromegaly, thyroid lesions). (1|++++)

Special Populations/Considerations

The Task Force recommends urgent treatment (within 24–72 hours) of hypercortisolism if life-threatening complications of CS such as infection, pulmonary thromboembolism, cardiovascular complications, and acute psychosis are present. (1|+++O). The associated disorder(s) should be addressed as well (e.g., anticoagulation, antibiotics).

Definitions

Quality of the Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendations

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

### Clinical Algorithm(s)

An algorithm titled "An Algorithm for the Treatment of CS" is provided in the original guideline document.

## Scope

### Disease/Condition(s)

Cushing's syndrome (CS)

### Guideline Category

Evaluation

Management

Treatment

### Clinical Specialty

Endocrinology

Internal Medicine

Pediatrics

Surgery

### Intended Users

Physicians

### Guideline Objective(s)

To formulate clinical practice guidelines for treating Cushing's syndrome (CS)

## Target Population

Pediatric and adult patients with Cushing's syndrome (CS)

## Interventions and Practices Considered

1. Establishing treatment goals
    - Normalizing cortisol levels or action at its receptors
    - Treatment of comorbidities associated with hypercortisolism
    - Treatment to reduce cortisol levels or action if there is not an established diagnosis of Cushing's syndrome (CS) (not recommended)
2. Adjunctive management
    - Providing education to patients/families/caretakers
    - Monitoring and adjunctive treatment for cortisol-dependent comorbidities (psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness)
    - Use of a multidisciplinary team
    - Evaluation for risk factors for venous thrombosis and perioperative prophylaxis for venous thromboembolism
    - Age-appropriate vaccinations
3. First-line treatment
    - Resection of primary lesion(s) (unilateral resection, localizing and resecting ectopic adrenocorticotropic hormone [ACTH]-secreting tumors with node dissection, transsphenoidal selective adenomectomy [TSS])
    - Measurement of serum sodium several times after TSS
    - Assessment of free thyroxine ($T_4$) and prolactin after surgery to evaluate for overt hypopituitarism
    - Postoperative pituitary magnetic resonance imaging (MRI) scan after successful TSS
    - Surgical resection of bilateral adrenal disorders and medical therapy to block aberrant hormone receptors for bilateral macronodular adrenal hyperplasia
4. Management of remission and recurrence after surgical resection
5. Glucocorticoid replacement and discontinuation, and resolution of other hormonal deficiencies
6. Second-line treatment
    - Shared decision-making approach
    - Bilateral adrenalectomy
    - Repeat TSS
    - Radiation therapy (RT)/radiosurgery (RS)
    - Medical treatment (steroidogenesis inhibitors, pituitary-directed medical treatments, glucocorticoid antagonist, targeted therapies to treat ectopic ACTH syndrome)
7. Approach for long-term follow-up
8. Special populations/considerations (infection, pulmonary thromboembolism, cardiovascular complications, and acute psychosis)

## Major Outcomes Considered

- Biochemical remission
- Biochemical recurrence rates

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

The Task Force commissioned three systematic reviews and used the best available evidence from other published systematic reviews and

individual studies.

The three systematic reviews summarized data from 29 case series of radiation therapy (RT) in Cushing's disease (CD), 21 case series of radiosurgery in CD, and 87 case series of treatment-naive CD patients who received first-line transsphenoidal surgery. The outcomes of interest were biochemical remission and biochemical recurrence rates.

Methods

For all three systematic reviews, the search included the electronic databases MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews, CINAHL, and Scopus. The Task Force expanded the search to include all languages, with latest date of inclusion to be August 2013. Abstracts and titles that resulted from executing the search strategy were independently evaluated by two reviewers for potential eligibility and the full text versions of all potentially eligible studies were obtained. Two reviewers working independently considered the full text reports for eligibility. Disagreements were harmonized by consensus and if not possible by consensus through arbitration by a third reviewer.

Radiosurgery in Patients with Cushing's Disease: Systematic Review and Meta-analysis

The Task Force searched for comparative studies and when not possible, they included singles arms from studies that reported outcomes of interest in patients who received radiosurgery (RS). Radiosurgical techniques included mainly Gamma knife techniques (cobalt, stereotactic, leksell, linear accelerator [LINAC], proton beam). Biochemical remission and recurrence were defined by various criteria, and therefore, were also reported according to the used definitions.

Radiotherapy in Patients with Cushing's Disease: Systematic Review and Meta-analysis

The Task Force searched for comparative studies and when not possible, they included singles arms from studies that reported treatment-naïve interventions of interest. They included any form of RT, including conventional, external beam, fractioned, heavy particle and LINAC RT. Biochemical remission and recurrence were defined by various criteria, and therefore, were reported according to the used definitions.

Transsphenoidal Surgery in Treatment-naïve Patients with Cushing's Disease: Systematic Review and Meta-analysis

The Task Force searched for comparative studies and when not possible, they included singles arms from studies that reported treatment-naïve surgical interventions. No criteria restrictions were pre-defined for remission or recurrent outcomes.

## Number of Source Documents

Radiosurgery in Patients with Cushing's Disease: Systematic Review and Meta-analysis

The initial search resulted in 1261 citations and after abstract review this was limited to 217 potentially relevant articles which were obtained. These were reviewed in full-text by two reviewers and 21 were included with 196 being excluded. There were 14 studies that enrolled adult patients, one study with pediatric sub-population (Levy 1991), and seven with mixed population.

Radiotherapy in Patients with Cushing's Disease: Systematic Review and Meta-analysis

The initial search resulted in 1261 citations and after abstract review this was limited to 217 potentially relevant articles which were obtained. These were reviewed in full-text by two reviewers and 29 were included with 188 being excluded.

Transsphenoidal Surgery in Treatment-naïve Patients with Cushing's Disease: Systematic Review and Meta-analysis

The initial search resulted in 1261 citations and after abstract review this was limited to 145 potentially relevant articles which were obtained and two more were identified through reference review of the selected articles. These were reviewed in full-text by two reviewers and 87 were included with 58 being excluded.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Quality of the Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

## Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Methods

Overall, analyses were underpowered to determine important independent predictors of the outcomes of interest. The quality of the evidence for recurrence and remission outcomes was low due to high risk of bias, heterogeneity, and imprecision.

Using a standardized form two reviewers independently extracted data from each study and later reconciled differences, if present. Reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data.

To measure the overall heterogeneity across the included studies, the reviewers used $I^2$ statistic, where $I^2$ >50% suggests high heterogeneity. All statistical analyses were conducted using STATA version 12.1 (StataCorp LP, College Station, Texas).

Radiosurgery in Patients with Cushing's Disease: Systematic Review and Meta-analysis

The outcome measure was the event rate (cumulative incidence) at the end of follow up period. The 95% confidence intervals were estimated using binomial distribution. The reviewers then pooled the log transformed event rates using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model. The Altman and Bland test was used to compare the outcomes in the subgroup surgical interventions, when possible. They conducted subgroup analyses based on follow-up period, history of magnetic resonance imaging (MRI) use (initial/pre-treatment, follow-up/post-treatment, or both), history of receiving prior transsphenoidal surgery (TSS), gender, age groups (pediatric vs. adult), tumor size (micro- vs. macroadenoma), dural invasion (yes or no), and year of publication (pre- and post-1975).

Radiotherapy in Patients with Cushing's Disease: Systematic Review and Meta-analysis

The outcome measure was the event rate (cumulative incidence) at the end of follow-up period. The 95% confidence intervals were estimated using binomial distribution. The reviewers then pooled the log transformed event rates using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model. The Altman and Bland test was used to compare the outcomes in the subgroup surgical interventions, when possible. They conducted subgroup analyses based on follow-up period, history of MRI use (initial/pre-treatment, follow-up/post-treatment, or both) and history of receiving prior TSS, gender, age groups (pediatric vs. adult), tumor size (micro- vs. macroadenoma), dural invasion (yes or no), year of publication (pre- and post-1975), the number of biochemical diagnostic tests used (single vs. multiple), and radiation dose (<45 GY, 45-50 GY, or >50GY).

Transsphenoidal Surgery in Treatment-naïve Patients with Cushing's Disease: Systematic Review and Meta-analysis

The main outcome measure was the event rate at the longest study follow up period (cumulative incidence). The 95% confidence intervals were estimated using binomial distribution. The reviewers then pooled the log transformed event rates using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model. They pooled effect size using the DerSimonian and Laird random-effect models. The Altman and Bland test was used to compare the outcomes in the subgroup surgical interventions, when possible. The reviewers conducted subgroup analyses based on follow-up period, surgeon's experience (one surgeon performing the surgery vs. multiple), age groups (pediatric vs. adults), adenoma size (micro- vs. macroadenoma), adenoma histology (positive vs. negative), gender, type of surgery, dural invasion, and the pre-operative diagnosis with MRI to assess the effect of these predictors, when possible.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Participants

Participants included an Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. The European Society for Endocrinology co-sponsored the guideline.

Evidence

The Task Force used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process

The Task Force achieved consensus through one group meeting, several conference calls, and numerous e-mail communications. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

## Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

Internal Peer Review

## Description of Method of Guideline Validation

Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

# Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

- Treatment of Cushing's syndrome (CS) is essential to reduce mortality and associated comorbidities.
- Restoring eucortisolism leads to clinical and biochemical improvements regarding obesity, arterial hypertension, insulin resistance, glucose tolerance, dyslipidemia, bone mineral density (BMD), linear growth in children, cognition, psychiatric disorders, and health-related quality of life (HRQOL).

### Potential Harms

- Because all treatments carry risk, clinicians should establish a diagnosis of Cushing's syndrome (CS) before administering them.
- Adverse side effects of medications used to treat CS (see Table 1 in the original guideline document for common side effects of specific medications)
- As with any transsphenoidal selective adenomectomy (TSS), potential complications include electrolyte disturbances, hemorrhage, and meningitis. Hyponatremia occurs in 5%–10% of patients, usually between postoperative days 5 and 10. This complication is more common after extensive gland exploration in menstruating women. Diabetes insipidus is relatively common in the first few postoperative days but is usually transient. The Task Force recommends measuring serum sodium several times during the first 5–14 days after surgery to address both possibilities, either daily or guided by the patient's intake and output.
- Despite the use of physiological glucocorticoid replacement, many patients suffer from glucocorticoid withdrawal after surgery. Patients should be warned that this is common and expected. Symptoms include anorexia; nausea; weight loss; and other nonspecific symptoms such as fatigue, flu-like myalgias and arthralgias, lethargy, and skin desquamation. Accordingly, patients usually feel worse within a few days or weeks after successful surgery. Adults may experience persistent or new-onset atypical depressive disorders, anxiety, or panic symptoms. Recovery from the glucocorticoid withdrawal syndrome may take 1 year or longer.
- Hypopituitarism is a risk with all forms of radiation. Up to two-thirds of patients develop anterior pituitary hormone deficiency after radiation therapy (RT). Additional radiation risks include optic neuropathy (1%–2%) and other cranial neuropathies (2%–4%) as well as a small risk of secondary neoplasia within the radiation field (most commonly meningiomas).

## Qualifying Statements

### Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Getting Better

Living with Illness

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31. [213 references] PubMed

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2015 Aug

## Guideline Developer(s)

The Endocrine Society - Professional Association

## Source(s) of Funding

The Endocrine Society was the only funding source for this guideline; the Task Force received no funding or remuneration from commercial or other entities.

## Guideline Committee

Treatment of Cushing's Syndrome Task Force

## Composition of Group That Authored the Guideline

*Task Force Members*: Lynnette K. Nieman (*Chair*), Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, Antoine Tabarin

## Financial Disclosures/Conflicts of Interest

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest. These are reviewed before members are approved to serve on the Task Force and reviewed periodically during the development of the guideline. The Clinical Guidelines Subcommittee vets the conflict-of-interest forms before the members are approved by the Society's Council to participate on the guideline Task Force. Most participants who help develop the guideline must have no conflict of interest related to the matter under study.

Those participants who do have conflicts of interest must disclose all conflicts. The Clinical Guidelines Subcommittee and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest. Most members of the Task Force have relationships with companies that make pharmaceuticals for the treatment of Cushing's syndrome (CS). The Task Force explicitly discussed the possibility of a perception of conflict and agreed that the sections on individual pharmaceuticals would be written by an individual without such a conflict; subsequent changes were approved by the entire group.

Conflicts of interest are defined as receiving any compensation from commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (e.g., stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Financial Disclosures of the Task Force*

Lynnette K. Nieman, MD (Chair) - Financial or Business/Organizational Interests: UpToDate; Significant Financial Interest or Leadership Position: HRA Pharma (Research Grant to Institution), UpToDate (Honoraria).

Beverly M. K. Biller, MD - Financial or Business/Organizational Interests: American Association of Clinical Endocrinologist, Growth Hormone Research Society, American College of Physicians; Significant Financial Interest or Leadership Position: HRA Pharma (Consultant), Cortendo (Consultant, Research Grant to Institution), Novartis (Consultant, Research Grant to Institution), Novo Nordisk (Consultant, Research Grant to Institution), Pfizer (Consultant).

James W. Findling, MD - Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: Novartis (Consultant, Research Grant to Institution), Corcept (Consultant, Research Grant to Institution).

Hassan M. Murad**, MD, MPH - Financial or Business/Organizational Interests: Mayo Clinic, Division of Preventive Medicine; Significant Financial Interest or Leadership Position: none declared.

John Newell-Price, MD, FRCP, PhD - Financial or Business/Organizational Interests: Royal College of Physicians, Society of Endocrinology, The Pituitary Foundation; Significant Financial Interest or Leadership Position: Novartis (Consultant, Study Steering Committee), HRA Pharma (Consultant, Research Grants), Clinical Endocrinology (Senior Editor).

Martin O. Savage, MD, FRCPCH - Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: IPSEN (Consultant), Merke Serono (Consultant), Sandoz (Consultant), OPKO Health, Inc. (Consultant).

Antoine Tabarin, MD - Financial or Business/Organizational Interests: Novartis, HRA Pharma; Significant Financial Interest or Leadership Position: Novartis (Board, Speaker, Honoraria, Research Grant to Institution), HRA Pharma (Speaker, Honoraria, Research Grant to Institution), IPSEN Biotech (Speaker, Honoraria).

* Financial, business, and organizational disclosures of the task force cover the year prior to publication. Disclosures prior to this time period are archived.

**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.

## Guideline Endorser(s)

European Society of Endocrinology - Medical Specialty Society

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from The Endocrine Society Web site.

## Availability of Companion Documents

The following is available:

- Dabrh AM, Singh Ospina NM, Nofal AA, Farah WH, Barrionuevo P, Sarigianni M, Mohabbat AB, Benkhadra K, Carranza Leon BG, Gionfriddo MR, Wang Z, Mohammed K, Ahmed A, Elraiyah TA, Haydour Q, Alahdab F, Prokop LJ, Murad MH. Predictors of biochemical remission and recurrence after surgical and radiation treatments of Cushing's disease: a systematic review and meta-analysis. Endocr Pract. 2016 Jan 20. (Epub ahead of print). Available from the American Association of Clinical Endocrinologists (AACE) Journals Endocrine Practice Web site.

## Patient Resources

None available

## NGC Status

This NGC summary was completed by ECRI Institute on December 7, 2015. The information was not verified by the guideline developer.

## Copyright Statement



# Disclaimer

## NGC Disclaimer

Readers with questions regarding guideline content are directed to contact the guideline developer.